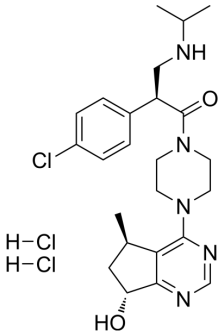
Ipatasertib dihydrochloride

Cat. No.:	HY-15186A
CAS No.:	1396257-94-5
Molecular Formula:	$C_{24}H_{34}Cl_3N_5O_2$
Molecular Weight:	530.92
Target:	Akt; Organoid
Pathway:	PI3K/Akt/mTOR; Stem Cell/Wnt
Storage:	4°C, sealed storage, away from moisture * In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (188.35 mM; Need ultrasonic)

H_2O : ≥ 41 mg/mL (77.22 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.8835 mL	9.4176 mL	18.8352 mL
5 mM	0.3767 mL	1.8835 mL	3.7670 mL
10 mM	0.1884 mL	0.9418 mL	1.8835 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: PBS
   Solubility: 16.67 mg/mL (31.40 mM); Clear solution; Need ultrasonic
2. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: ≥ 3.88 mg/mL (7.31 mM); Clear solution
3. Add each solvent one by one: 5% DMSO >> 95% (20% SBE-β-CD in saline)
   Solubility: ≥ 3.88 mg/mL (7.31 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (3.92 mM); Clear solution
5. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (3.92 mM); Clear solution
6. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (3.92 mM); Clear solution

BIOLOGICAL ACTIVITY

Description	Ipatasertib dihydrochloride (GDC-0068 dihydrochloride) is a highly selective and ATP-competitive pan-Akt inhibitor with IC_{50}s of 5, 18 and 8 nM for Akt1, Akt2 and Akt3, respectively.

IC_{50} & Target			
Akt1 5 nM (IC_{50})	Akt3 8 nM (IC_{50})	Akt2 18 nM (IC_{50})	PKA 3100 nM (IC_{50})

In Vitro

Ipatasertib shows more than 600 and more than 100-fold selectivity for Akt1 in IC_{50} against the closely related kinases PKA and p70S6K, respectively. When tested at 1 μM in a panel of 230 protein kinases, which includes 36 human AGC family members, Ipatasertib inhibits only 3 other kinases by more than 70% at 1 μM concentration (PRKG1α, PRKG1β, and p70S6K). IC_{50}s measured for these 3 kinases are 98, 69, and 860 nM, respectively. Thus, with the exception of PKG1 (relative to which Ipatasertib is >10-fold more selective for Akt1), Ipatasertib displays a more than 100-fold selectivity for Akt1 over the next most potently inhibited non-Akt kinase, p70S6K, in the screening kinase panel. The relationship between pharmacokinetics (PK) and pharmacodynamics (PD) of Ipatasertib is investigated in 3 xenograft models that showed dose-dependent response to drug treatment: MCF7-neo/HER2, TOV-21G.x1, and LNCaP. The mean cell viability IC_{50} of Ipatasertib in these 3 cell lines is 2.56, 0.44, and 0.11 μM, respectively[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

Ipatasertib is typically efficacious in xenograft models in which Akt is activated because of genetic alterations including PTEN loss, PIK3CA mutations/amplifications, or HER2 overexpression. In these models, tumor growth delay, stasis, or regression is achieved at or below 100 mg/kg daily oral dose, which is the maximum dose tested in immunocompromised mice that is well tolerated. When tested in vivo, daily dosing of Ipatasertib in combination with RP-56976 induces tumor regression and stasis in the PC-3 and MCF7-neo/HER2 xenograft models, at doses where each single agent is ineffective or only causes modest tumor growth delay. Similarly, increased TGI is observed in the OVCAR3 ovarian cancer xenograft model when Ipatasertib is combined with NSC 241240. The combination of Ipatasertib with RP-56976 or NSC 241240 is tolerated with less than 5% body weight loss when compared with treatment with each chemotherapeutic agent alone[2].

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PROTOCOL

Cell Assay [2]

The 384-well plates are seeded with 2,000 cells per well in a volume of 54 μL per well followed by incubation at 37°C under 5% CO_2 overnight (~16 hours). Compounds (e.g., Ipatasertib) are diluted in DMSO to generate the desired stock concentrations then added in a volume of 6 μL per well. All treatments are tested in quadruplicates. After 4 days incubation, relative numbers of viable cells are estimated using CellTiter-Glo and total luminescence is measured on a Wallac Multilabel Reader. The concentration of drug resulting in IC_{50} is calculated from a 4-parameter curve analysis (XLfit) and is determined from a minimum of 3 experiments. For cell lines that failed to achieve an IC_{50}, the highest concentration tested (10 μM) is listed[2].

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Animal Administration [2]

Mice[2]

In vivo efficacy is evaluated in multiple tumor cell line- and patient-derived xenograft models. Cells or tumor fragments are implanted subcutaneously into the flank of immunocompromised mice. Female or male nude (nu/nu) or severe combined immunodeficient mice (SCID)/beige mice are used. The LuCaP35V patient-derived primary tumors are obtained; male mice are castrated before implantation of tumor fragments. After implantation of tumor cells or fragments into mice, tumors are monitored until they reached mean tumor volumes of 180 to 350 mm^3 and distributed into groups of 8 to 10 animals/group. Ipatasertib is formulated in 0.5% methylcellulose/0.2% Tween-80 (MCT) and administered daily (QD), via oral (per os; PO) gavage. RP-56976 is formulated in 3% EtOH/97% saline and dosed intravenously (IV) every week (QW) at 2.5 or 7.5 mg/kg. NSC 241240 is formulated in saline and dosed intraperitoneally (IP) weekly at 50 mg/kg.

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell Metab. 2021 Nov 2;33(11):2247-2259.e6.
- Blood. 2023 May 26;blood.2022018752.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Mol Cell. 2020 Sep 17;79(6):1008-1023.e4.
- Mol Cell. 2019 Jan 3;73(1):22-35.e6.

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REFERENCES

[1]. Blake JF, et al. Discovery and preclinical pharmacology of a selective ATP-competitive Akt inhibitor (GDC-0068) for the treatment of human tumors. J Med Chem. 2012 Sep 27;55(18):8110-27.

[2]. Lin J, et al. Targeting activated Akt with GDC-0068, a novel selective Akt inhibitor that is efficacious in multiple tumor models. Clin Cancer Res. 2013 Apr 1;19(7):1760-72.

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